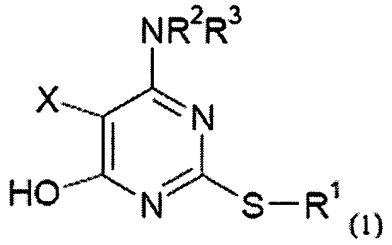
10/525495
DT01 Rec'd PCT/PTO 23 FEB 2005

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A compound of formula (1), a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof:



(1)

wherein R^1 is a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, nitrile, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, phenyl or heteroaryl; wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

wherein R^2 is C_{3-7}carbocyclyl, optionally substituted by 1, 2 or 3 substituents independently selected from:

(a) fluoro, $-OR^4$, $-NR^5R^6$ $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$;

(b) a 3-8 membered ring optionally containing 1, 2 or 3 atoms selected from O, S, $-NR^8$ and whereby the ring is optionally substituted by C_{1-3}alkyl or fluoro; or

(c) phenyl or heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, -OR^4, -NR^5R^6, -$CONR^5R^6$, -NR^8COR^9, -$SO_2NR^5R^6$, -$NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

or R^2 is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl wherein the group is substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6} alkyl)-*N*–(phenyl)amino, *N*- C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6} alkyl)$_2$carbamoyl, *N*-(C_{1-6} alkyl)-*N*–(phenyl)carbamoyl, carboxy, phenoxycarbonyl, –NR^8COR^9, -SO_2R^{10}, –$SO_2NR^5R^6$ and –$NR^8SO_2R^9$;

wherein R^3 is hydrogen or R^2;

R^4 is hydrogen or a group selected from C_{1-6}alkyl and phenyl, wherein the group is optionally substituted by 1 or 2 substituents independently selected from halo, phenyl, -OR^{11} and -$NR^{12}R^{13}$;

R^5 and R^6 are independently hydrogen or a group selected from C_{1-6}alkyl and phenyl wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, -OR^{14},-$NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$SONR^{15}R^{16}$ and $NR^{15}SO_2R^{16}$

or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by 1, 2 or 3 substituents independently selected from phenyl, -OR^{14}, -$COOR^{14}$, -$NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$ or C_{1-6}alkyl, (optionally substituted by 1 or 2 substituents independently selected from halo, –$NR^{15}R^{16}$ and -OR^{17} groups);

R^{10} is hydrogen or a group selected from C_{1-6}alkyl or phenyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, -OR^{17} and -$NR^{15}R^{16}$;

and

each of R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14} R^{15}, R^{16}, R^{17} is independently hydrogen, C_{1-6}alkyl or phenyl;

X is hydrogen, halo, cyano, nitro, hydroxy, C_{1-6}alkoxy, (optionally substituted by 1 or 2 substituents selected from halo, -OR^{11} and -$NR^{12}R^{13}$), -NR^5R^6, -$COOR^7$, -$CONR^5R^6$, -NR^8COR^9, thio, thiocyano, thio C_{1-6}alkyl, (optionally substituted by 1 or 2 substituents selected from halo,

$-OR^{17}$, $-COOR^{7}$,$-NR^{15}R^{16}$, $-CONR^{5}R^{6}$, $-SO_2R^{10}$, $-SO_2NR^{5}R^{6}$ $-NR^{8}SO_2R^{10}$ or a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, $-OR^{4}$, $-NR^{5}R^{6}$, $-CONR^{5}R^{6}$, $-COOR^{7}$, $-NR^{8}COR^{9}$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^{5}R^{6}$ and $-NR^{8}SO_2R^{9}$; or a -phenyl, -heteroaryl, -thiophenyl, -thioheteroaryl, aminoheteroaryl, and thio C_{1-6}alkylheteroaryl group, all of which may be optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^{4}$, $-NR^{5}R^{6}$, $-CONR^{5}R^{6}$, $-COOR^{7}$, $-NR^{8}COR^{9}$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^{5}R^{6}$, $-NR^{8}SO_2R^{9}$, C_1-C_6alkyl, phenyl, heteroaryl or trifluoromethyl groups;

2. (Currently amended) A compound according to claim 1 or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, wherein R^{1} is C_{1-8}alkyl optionally substituted by 1, 2 or 3 substituents independently selected from phenyl or heteroaryl, wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, $-OR^{4}$, $-SR^{10}$, C_{1-6}alkyl and trifluoromethyl.

3. (Currently amended) A compound according to claim 1 or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, wherein R^{2} is C_{1-8}alkyl substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)-*N* –(phenyl)amino, *N*- C_{1-6}alkylcarbamoyl, *N,N*-di(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)-*N* –(phenyl)carbamoyl, carboxy, phenoxycarbonyl, $-NR^{8}COR^{9}$, $-SO_2R^{10}$, $-SO_2NR^{5}R^{6}$ and $-NR^{8}SO_2R^{9}$; and wherein R^{3} is hydrogen;

4. (Currently amended) A compound according to claim 1 or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, wherein R^{4}, R^{5}, R^{6}, R^{8}, R^{9} and R^{10} are independently hydrogen, C_{1-4}alkyl or phenyl.

5. (Currently amended) A compound according to claim 1 or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, wherein X is hydrogen, halo, cyano, nitro,

hydroxy, thio, thiocyano, -$CONR^5R^6$, thio C_{1-6}alkyl, (optionally substituted by 1 or 2 substituents selected from halo, -OR^{17}, -$NR^{15}R^{16}$, -$CONR^5R^6$), -$NR^8SO_2R^{10}$, C_{1-8}alkyl, (optionally substituted by 1, 2 or 3 substituents independently selected from halo, -OR^4, -NR^5R^6, -$CONR^5R^6$, -$COOR^7$, -NR^8COR^9, -SR^{10}, -SO_2R^{10}, -$SO_2NR^5R^6$ and -$NR^8SO_2R^9$), heteroaryl, thioheteroaryl or thioC_{1-6}alkylheteroaryl all of which may be optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, -OR^4, -NR^5R^6, -$CONR^5R^6$, -$COOR^7$, NR^8COR^9, -SR^{10}, -SO_2R^{10}, -$SO_2NR^5R^6$, -$NR^8SO_2R^9$, C_{1-6}alkyl or trifluoromethyl.

6. (Currently amended) A compound according to claim 2 or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, wherein R^1 is benzyl optionally substituted by 1 or 2 substituents independently selected from fluoro, chloro, bromo, methoxy, methyl and trifluoromethyl.

7. (Currently amended) A compound according to claim 3 or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, wherein R^2 is C_{1-4}alkyl, substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, and di(C_{1-6}alkyl)amino; and R^3 is hydrogen.

8. (Currently amended) A compound according to claim 4 or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, wherein X is hydrogen, fluoro, chloro, bromo, thiocyano, -$NR^8SO_2R^9$, (where R^8 is hydrogen and R^9 is methyl), –thioimidazolyl, -thiotriazolyl, -$CONH_2$, -$CONMe_2$ or cyano.

9. (Original) A compound selected from the group consisting of:
2-(Benzylthio)-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol,
2-(Benzylthio)-5-chloro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol,
2-[(3-Chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol,
5-Chloro-2-[(3-chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol,

2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl thiocyanate,

N-(2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl)methanesulfonamide,

2-[(3-Chlorobenzyl)thio]-5-fluoro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol, 2-[(2,3-difluorobenzyl)thio]-4-hydroxy-6{[(1S)-2-hdroxy-1-methylethyl]amino}pyrimidine-5-carbonitrile,

5-Chloro-2-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-4-pyrimidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-iodo-4-pyrimidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-nitro-4-pyrimidinol,

2-[[(3-Chlorophenyl)methyl]thio]-6-[[(1R)2-hydroxy-1-methylethyl]amino]-5-(1,3,4-thiadiazol-2-ylthio)-4-pyrimidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1R)-2-hydroxy-1-methylethyl]amino]-5-(1*H*-imidazol-2-ylthio)-4-pyrmidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-5-[[2-(dimethylamino)ethyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-4-pyrimidinol,

1-[2-[[(2,3-Difluorophenyl)methyl]thio]-4-hydroxy-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-pyrimidinyl]- 4(1*H*)-pyridinethione,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-(4-pyridinylthio)- 4-pyrimidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-(1*H*-1,2,4-triazol-3-ylthio)- 4-pyrimidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]- 4-pyrimidinol,

5-[(5-Amino-4*H*-1,2,4-triazol-3-yl)thio]-2-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-

hydroxy-1-methylethyl]amino]- 4-pyrimidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[[5-(4-pyridinyl)-1,3,4-oxadiazol-2-yl]thio]- 4-pyrimidinol,

Ethyl[[2-[[(2,3-difluorophenyl)methyl]thio]-4-hydroxy-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-pyrimidinyl]thio]- AcOH,

2-[[2-[[(2,3-Difluorophenyl)methyl]thio]-4-hydroxy-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-pyrimidinyl]thio]-*N*-methyl- acetamide,

2-[[2-[[(2,3-Difluorophenyl)methyl]thio]-4-hydroxy-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-pyrimidinyl]thio]-*N*-[2-(dimethylamino)ethyl]- acetamide,

1-[[[2-[[(2,3-Difluorophenyl)methyl]thio]-4-hydroxy-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-pyrimidinyl]thio]acetyl]-piperazine,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(4-methyl-2-oxazolyl)thio]- 4-pyrimidinol,

2-[[(2,3-Difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-5-[(1,2,4-oxadiazol-3-ylmethyl)thio]- 4-pyrimidinol,

2-[(2,3-difluorobenzyl)thio]-4-{[(1*R*)-1,2-dihydroxyethyl]amino}-6-hydroxypyrimidine-5-carboxamide,

2-[(2,3-difluorobenzyl)thio]-6-{[(1*R*)-2-hydroxy-1-methylethyl]amino}-5-(5-methyl-1,2,4-oxadiazol-3-yl)pyrimidin-4-ol,

2-[(2,3-difluorobenzyl)thio]-6-{[(1*R*)-2-hydroxy-1-methylethyl]amino}-5-(1,3-oxazol-5-yl)pyrimidin-4-ol,

2-[(2,3-difluorobenzyl)thio]-4-{[(1*R*)-1,2-dihydroxyethyl]amino}-6-hydroxy-*N*,*N*-dimethylpyrimidine-5-carboxamide,

2-[(2,3-difluorobenzyl)thio]-5-fluoro-6-{[(1*R*)-2-hydroxy-1-methylethyl]amino}-pyrimidin-4-ol,

2-[(3,4-difluorobenzyl)thio]-5-fluoro-6-{[(1*R*)-2-hydroxy-1-methylethyl]amino}-pyrimidin-4-ol,

2-[(3-fluorobenzyl)thio]-5-fluoro-6-{[(1*R*)-2-hydroxy-1-methylethyl]amino}pyrimidin-4-ol,

or

2-[(4-fluorobenzyl)thio]-5-fluoro-6-{[(1*R*)-2-hydroxy-1-methylethyl]amino}pyrimidin-4-ol and

a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof.

10. (Cancelled)

11. (Currently amended) A method of treating~~, compound, pharmaceutically acceptable salt, solvate, or in vivo hydrolysable ester thereof according to any one of claims 1 to 9 for use as a medicament for the treatment of~~ asthma, allergic rhinitis, COPD, inflammatory bowel disease, osteoarthritis, osteoporosis, rheumatoid arthritis, or psoriasis comprising administering a compound of claim 1, or a pharmaceutically acceptable salt, solvate or in vivo hydrolysable ester thereof.

12. (Currently amended) A method of treating cancer, comprising administering a compound of claim 1, or a pharmaceutically acceptable salt, solvate or in vivo hydrolysable ester thereof. ~~, pharmaceutically acceptable salt, solvate, or in vivo hydrolysable ester thereof according to any one of claims 1 to 9 for use as a medicament for the treatment of cancer.~~

13. (Currently amended) A method of treating COPD comprising administering a compound of claim 1, or a pharmaceutically acceptable salt, solvate or in vivo hydrolysable ester thereof.. ~~, pharmaceutically acceptable salt, solvate, or in vivo hydrolysable ester thereof according to any one of claims 1 to 9 for use as a medicament for the treatment of COPD.~~

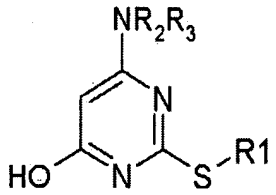
14. (Currently amended) A method of treating a disease or condition ~~The use of a compound, pharmaceutically acceptable salt, solvate, or in vivo hydrolysable ester thereof according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of human diseases or conditions~~ in which modulation of chemokine receptor activity is beneficial, comprising administering a compound of claim 1, or a pharmaceutically acceptable salt, solvate or in vivo hydrolysable ester thereof.

15-16. (Cancelled)

17. (Currently amended) A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, solvate, or in vivo hydrolysable ester thereof according to ~~any one of claims 1 to 9~~claim 1; and a pharmaceutically-acceptable diluent or carrier.

18. (Currently amended) A process for the preparation of a compound of formula (1) as defined above which comprises

(a) treating a compound of formula (2):



(2)

wherein R^1, R^2 and R^3 are as defined in claim 1, formula (1), with suitable electrophiles.

and optionally thereafter (i), (ii), (iii), (iv) or (v) in any order:

i) removing any protecting groups;

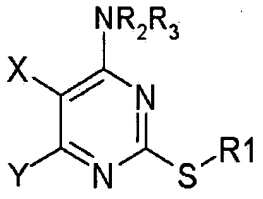
ii) converting the compound of claim 1, formula (1) into a further compound of claim 1, formula (1),

iii) forming a salt;

~~(~~iv) forming a prodrug

~~(~~v) forming an in vivo hydrolysable ester; or

(b) , where X is 1,3-oxazol-5-yl by treating a compound of formula (4):



(4)

wherein R^1, R^2 and R^3 are as defined in claim 1, formula (1), X is –CHO and Y is protected hydroxy by treatment with *p*-toluenesulfonylmethyl isocyanide and potassium hydroxide in refluxing methanol.

and optionally thereafter (i), (ii), (iii), (iv) or (v) in any order:

i) removing any protecting groups;

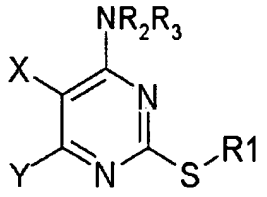
ii) converting the compound of claim 1, formula (1) into a further compound of claim 1, formula (1),

iii) forming a salt;

(iv) forming a prodrug,

v) forming an *in vivo* hydrolysable ester; or

(c) where X is CN by treating a compound of formula (4):



(4)

wherein R^1, R^2 and R^3 are as defined in claim 1, formula (1), X is CN and Y is halogen by treatment

with potassium *tert*-butoxide in refluxing aqueous toluene.

and optionally thereafter (i), (ii), (iii), (iv) or (v) in any order:

i) removing any protecting groups,

ii) converting the compound of claim 1, formula (1) into a further compound of claim 1, formula (1),

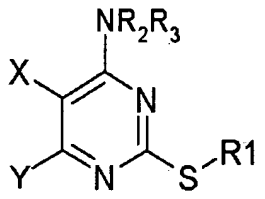
iii) forming a salt;

(iv) forming a prodrug,

v) forming an *in vivo* hydrolysable ester; or

(d) where X is $-CONR^5R^6$ by;

e) treating a compound of formula (4):



(4)

wherein R^1, R^2 and R^3 are as defined in claim 1, formula (1), X is $-CONR^5R^6$ and Y is halogen with a

suitable base.

and optionally thereafter (i), (ii), (iii), (iv) or (v) in any order:

i) removing any protecting groups;

ii) converting the compound of claim 1, formula (1) into a further compound of claim 1, formula (1),

iii) forming a salt;

(iv) forming a prodrug,

v) forming an *in vivo* hydrolysable ester.

19. (Currently amended) A ~~combination therapy~~ method of combination therapy which comprises administering a compound of claim 1, formula (1) or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, or a pharmaceutical composition or formulation comprising a compound of claim 1, formula (1), concurrently or sequentially with other therapy and/or another pharmaceutical agent.

20. (Currently amended) ~~A combination therapy as claimed in~~ The method of claim 19, comprising treating ~~for the treatment of~~ asthma, allergic rhinitis, COPD, inflammatory bowel disease, irritable bowel syndrome, osteoarthritis, osteoporosis, rheumatoid arthritis, or psoriasis.

21. (Currently amended) ~~A combination therapy as claimed in~~ The method of claim 19, comprising treating ~~for the treatment of~~ cancer.

22. (Currently amended) A pharmaceutical composition which comprises a compound of claim 1, formula (1) or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, in conjunction with another pharmaceutical agent.

23. (Currently amended) A method of treating ~~pharmaceutical composition as claimed in claim 22 for the treatment of~~ asthma, allergic rhinitis, COPD, inflammatory bowel disease, irritable bowel syndrome, osteoarthritis, osteoporosis, rheumatoid arthritis, or psoriasis, comprising administering the pharmaceutical composition of claim 22.

24. (Currently amended) A method of treating ~~pharmaceutical composition as claimed in claim 22 for the treatment of~~ cancer, comprising administering the pharmaceutical composition of claim 22.